DRUGS FOR LIVER DISEASES

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SEARCH ABOUT: DRUGS FOR HEPATIC DISORDERS

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INTERODUCTION

Liver is vital organ on human body and some other animal.
It is the largest organ in the body weighing 1200-1600gm .
Also, liver is one of the few organs which can regenerate after injury or disease.
It has a lot of important functions , some examples:

detoxification.

Protein synthesis.

Metabolizing of drugs.

Biochemical for digesting .

Manufacturing , breaking down &regulating numerous hormones.

☛ there are more than 500 functions of the liver!!!!!

So, any disorder affect liver causes a serious hazard on all the body.

Liver diseases:

Liver disease is categorized both by the cause and the effect it has on the liver. Causes may include infection, injury, exposure to drugs or toxic compounds, an autoimmune process, or a genetic defect that leads to the deposition and build-up of damaging substances such as iron or copper. Effects may

include inflammation, scarring, obstructions, clotting abnormalities, and liver failure.

Liver disease may not cause any symptoms at first or the symptoms may be vague, like weakness and loss of energy. In acute liver disease, symptoms related to problems handling bilirubin, including yellow skin and eyes (jaundice), dark urine, and light stools, along with loss of appetite, nausea, vomiting, and diarrhea are the most common. Chronic liver disease symptoms may include jaundice, dark urine, abdominal swelling (due to ascites), pruritus, unexplained weight loss or gain, and abdominal pain; these symptoms may not be present until the disease has reached an advanced stage.

Causes of liver disease:

1-Viral infection : ex. : Hepatitis A,B,C,D&E
2-Alcohol : ex.: alcoholic liver cirrhosis.
3-Vascular abnormalities: ex.: the Budd-Chiari syndrome "obstruction of the major hepatic veins leads to cell destruction and cirrhosis .
4-Inherited metabolic disorders
5-drugs and toxic.
6-Biliary tract disease
7-Infectious diseases.

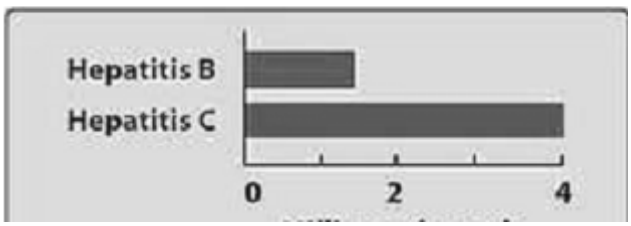
Drugs for Hepatic Viral Infection

The hepatitis viruses thus identified as ”A, B, C, D, and E”.

Each have a pathogenesis specifically involving replication in and destruction of hepatocytes. Of this group, hepatitis B and hepatitis C are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma ,and are the only hepatic viral infections for which therapy is currently available. [Note: Hepatitis A is a commonly encountered infection, but it is not a chronic disease.] Chronic hepatitis B is usually treated with peg interferon-α-2a, which is injected subcutaneously once weekly.

Oral therapy includes lamivudine, adefovir, enetecavir, or telbivudine. Combination therapy of an interferon plus lamivudine is no more effective than monotherapy with lamivudine.

Patients with acquired immunodeficiency syndrome (AIDS who are confected with hepatitis B are usually poor responders to interferon therapy.



The prevalence of chronic hepatitis B and C in the United States

A. Interferon:

Interferon is a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. Although interferon inhibits the growth of many viruses in vitro, its activity in vivo against viruses has been disappointing.

The interferons are synthesized by recombinant DNA technology. At least three types of interferon exist ,Int-α , Int-β ,Int-μ.

Interferon –α has been approved for treatment of hepatitis B and C, condylomata acuminata, and cancers such as hairy-cell leukemia and Kaposi's sarcoma.

In so-called oepagylated formulations, bis-monomethoxy polyethylene glycol has been covalently attached to either interferon α-2a or α-2b to increase the size of the molecule. The larger molecular size delays absorption from the injection site, lengthening the duration of action of the drug, and also decreases its clearance.

1. Mode of action: The antiviral mechanism is incompletely understood. It appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and t-RNA.

2. **Pharmacokinetics:** Interferon is not active orally, but it may be administered subcutaneously, or intravenously. Very little active compound is found in the plasma, and its presence is not correlated with clinical responses. Cellular uptake and

metabolism by the liver and kidney account for the disappearance of interferon from the plasma. Negligible renal elimination occurs.

3. Adverse effects: Adverse effects include flu-like symptoms on injection, such as fever, chills, myalgias, arthralgias, and gastrointestinal disturbances. Fatigue and mental depression are common. These symptoms subside with subsequent administrations. The principal dose-limiting toxicities are bone marrow suppression including granulocytopenia, neurotoxicity characterized by somnolence and behavioral disturbances, severe fatigue and weight loss, autoimmune disorders such as thyroiditis, and rarely, cardiovascular problems such as congestive heart failure.

Acute hypersensitivity reactions and hepatic failure are rare.

4. **Drug interactions:** Interferon interferes with hepatic drug metabolism, and toxic accumulations of theophylline have been reported. Interferon may also potentiate the myelosuppression caused by other bone marrow "depressing agents, such as zidovudine.

B. Lamivudine

This cytosine analog is an inhibitor of both hepatitis B virus (HBV), DNA polymerase and human immunodeficiency virus (HIV) reverse transcriptase.

1**-mode of action**: Lamivudine must be phosphorylated by host cellular enzymes to the triphosphate (active) form. This compound competitively inhibits HBV DNA polymerase at concentrations that

have negligible effects on host DNA polymerase. As with many nucleotide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life, which permit infrequent dosing.

Chronic treatment is associated with decreased plasma HBV DNA levels, improved biochemical markers, and reduced hepatic inflammation.

2-pharmacokinetic: Lamivudine is well absorbed orally and is widely distributed. Its plasma half-life is about 9 hours. Seventy percent is excreted unchanged in the urine. Dose reductions are necessary when there is moderate renal insufficiency (creatinine clearance less than 50 mL/min).

3-adverse effect: Lamivudine is well tolerated, with rare occurrences of headache and dizziness.

4-Example of drugs contain it:

Name: EPIVIR HBV®

Name: EPIVIR

C. Adefovir

1-**mode of action:** Adefovir dipivoxil is a nucleotide analog that is phosphorylated to adefovir diphosphate, which is then incorporated into viral DNA. This leads to termination of further DNA synthesis and prevents viral replication.

2-pharmacokinitics: Adefovir is administered once a day and is excreted in the urine, with 45 percent as the active compound. Clearance is influenced by renal function. Both decreased viral load and improved liver function have occurred in patients treated with adefovir.

3-**adverse effect:** As with other agents, discontinuation of adefovir results in sever exacerbation of hepatitis in about 25 percent of patients.

4-**Drug interaction** : adefovir does not seem to have significant drug interactions. The drug should be used cautiously in patients with existing renal dysfunction.

5-Brand name: *HEPSERA*® is the trade name for adefovir dipivoxil,

D. Entecavir

Entecavir is a guanosine analog approved for the treatment of HBV infections.

1-mode of action: following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral reverse transcriptase.

Entecavir has been shown to be effective against lamivudine-resister strains of HBV. Liver inflammation and scarring are improved.

Entecavir need only be given once a day.

3-**Pharmacokinitics:** entecavir undergoes both glomerular filtration and tubular secretion. Very little, if any, drug is metabolized. Renal function must be assessed periodically, and drugs that have renal toxicity should be avoided. Patients should be monitored closely for several months after discontinuation of therapy because of the possibility of severe hepatitis.

4-**Brand name:** *BARACLUDE®*

E. Telbivudine

Telbivudine is a thymidine analog that can be used in the treatment of HBV.

Unlike lamivudine and adefovir, telbivudine is not effective against HIV or other viruses.

1-Mode of action: The drug is phosphorylated intracellularly to the triphosphate, which can either compete with endogenous thymidine triphosphate for incorporation into DNA ,or else be incorporated into viral DNA, where it serves to terminate further elongation of the DNA chain. The drug administered orally, once a day, with or without food.

2-Pharmacokinitics: Telbivudine is eliminated by glomerular filtration as the unchanged drug, and no metabolites have been detected. The dose must be adjusted in renal failure.

"Combination of telbivudine with lamivudine has been no more effective than telbivudine alone."

3-Brand name: *Tyzeka*

Biphenyl dicarboxylate-DDP

1-Mechanism of action:

Acting as cell membrane stabilizer by blocker entrance of harmful toxins ,and helps to remove these toxin from liver cells.

2-Indication:

it has hepatoprotective, immunomodulator, anticarcinogenic and detoxifying effect.

3-Brand names:

a-DDP : b-Hepacare:

silymarin

It is the most famous constituent in drugs of hepatic disease.

So, we will talk about it in some details.

The flavonoid silymarin and one of its structural components, silibinin, are substances with documented hepatoprotective properties.

Silymarin is able to neutralise the hepatotoxicity of several agents, including *Amanita phalloides*, ethanol, paracetamol (acetaminophen) and carbon tetrachloride in animal models.

1-**Mode of action :**

Their mechanisms of action are still poorly understood. However, the data in the literature indicate that silymarin and silibinin act in four different ways: (i) as antioxidants, scavengers and regulators of the intracellular content of glutathione;

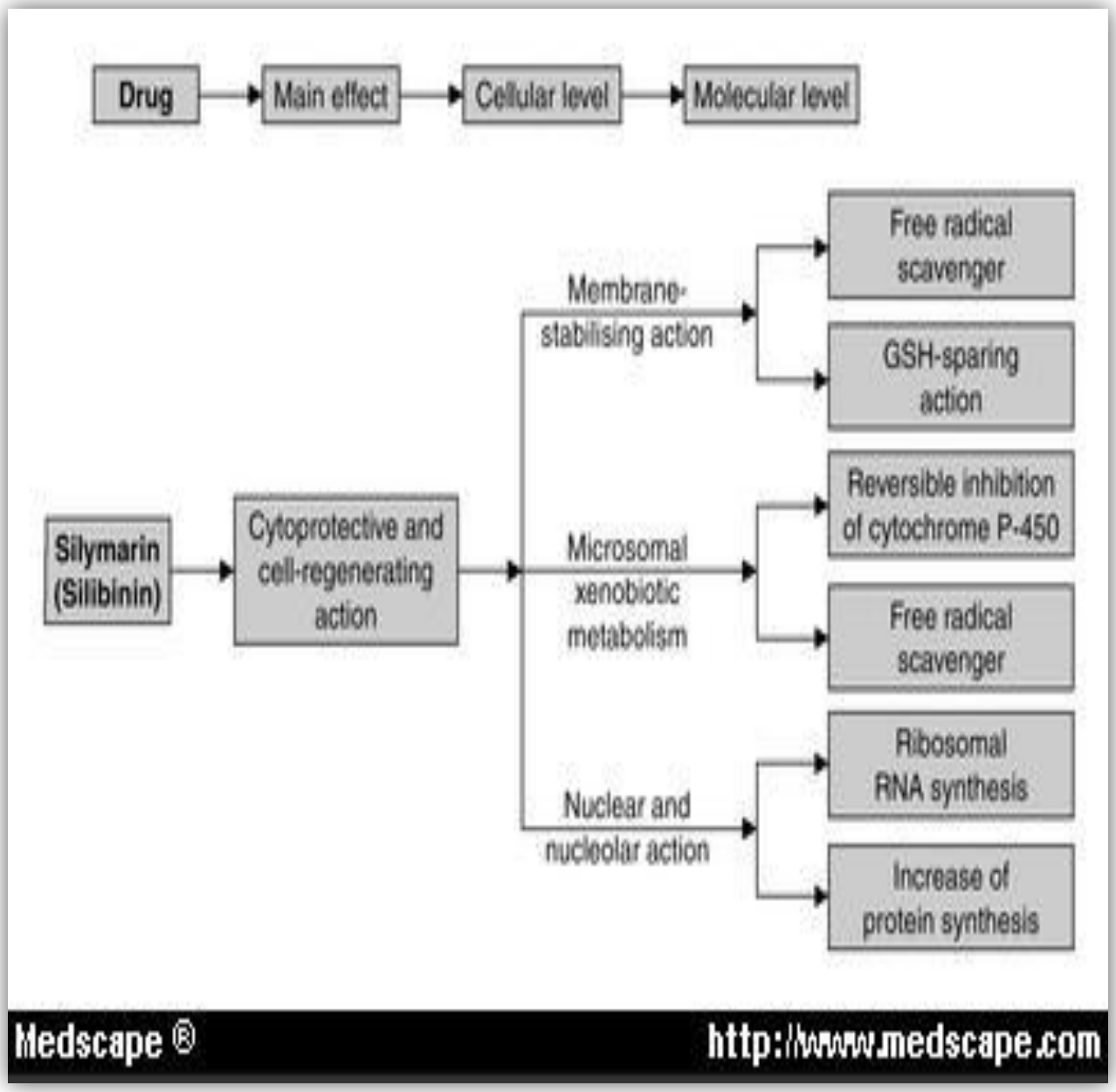
(ii) as cell membrane stabilizers and permeability regulators that prevent hepatotoxic agents from entering hepatocytes;

(iii) as promoters of ribosomal RNAsynthesis, stimulating liver regeneration.

(iv) as inhibitors of the transformation of stellate hepatocytes into myofibroblasts, the process responsible for the deposition of collagen fibers leading to cirrhosis.

The key mechanism that ensures hepatoprotection appears to be free radical scavenging. Anti-inflammatory and anticarcinogenic properties have also been documented.

"Mechanism of action of silymarin as proposed by Valenzuela and Garrido"



2-pharmacodynamic:

.A- Antioxidant Properties:

Flavonoids usually possess good antioxidant activity .The water-soluble dehydrosuccinate sodium salt of silibinin is a powerful inhibitor of the oxidation of linoleic acid-water emulsion catalysed by Fe^{2+} salts, It also inhibits in a concentration-dependent way the microsomal peroxidation produced by NADPH-Fe^{2+} -ADP, a well known experimental system for the formation of hydroxy radicals.

B- Activity against Lipid Peroxidation:-

Lipid peroxidation is the result of an interaction between free radicals of diverse origin and unsaturated fatty acids in lipids. Lipid peroxidation involves a broad spectrum of alterations, and the consequent degeneration of cell membranes may contribute towards the development of other disorders of lipoprotein metabolism, both in the liver and in peripheral tissues.

C-Effects on Liver Lipids:

The influence of silymarin on cellular permeability is closely associated with qualitative and quantitative alterations of membrane lipids (both cholesterol and phospholipids,] This suggests that silymarin may also act on other lipid compartments in the liver; this may influence lipoprotein secretion and uptake. It has been shown that silymarin and silibinin reduce the synthesis and turnover of phospholipids in the liver of rats.

D-Effects on Plasma Lipids and Lipoproteins:

The administration of silymarin reduces plasma levels of cholesterol and low-density lipoprotein (LDL) cholesterol in hyperlipidaemic rats, whereas silibinin does not reduce plasma levels of cholesterol in normal rats; however, it does reduce phospholipids' levels, especially those transported in LDL.

3-pharmacokinetic:

Silymarin is not soluble in water and is usually administered in capsules as a standard extract (70 to 80% silymarin). Absorption after oral administration is rather low, with recovery in the bile in rats ranging from 2 to 3%. Peak plasma concentrations are achieved in 4 to 6 hours, both in animal sand in humans. Silymarin is mainly excreted in the bile and, to a lesser degree, in the urine. Its elimination half-life ranges from 6 to 8 hours. However, other authors reported plasma levels of 500 mg/L (as silibinin) 90 minutes after oral administration of 200 mg/kg of silymarin or of purified *S marianum* extract in mice.

Silibinin and other components of silymarin are rapidly conjugated with sulfate and glucuronic acid in the liver. The conjugates pass into the plasma and into the bile, where they are found in amounts corresponding to 80% of the total dose administered

These findings suggest the existence of enterohepatic circulation: intestinal absorption, conjugation in the liver, excretion in the bile, hydrolysis by the intestinal flora, and reuptake in the intestine.

4-toxcicity:

The acute toxicity of silymarin has been studied in mice, rats, rabbits and dogs after intravenous infusion. The 50% lethal dose (LD50) values are 400 mg/kg in mice, 385 mg/kg in rats and 140 mg/kg in rabbits and dogs. However, these values are only approximate, as they depend on the infusion rate. When the compound is given by slow infusion (over 2 to 3 hours), values of 2 g/kg may be recorded in rats. After oral administration tolerance is even higher, with values over 10 g/kg. In the event of acute intoxication, the cause of death seems to be cardiovascular failure.

Names of some drugs:

1-Alpha Hepadox cap.>>>for hepatic protective and activity

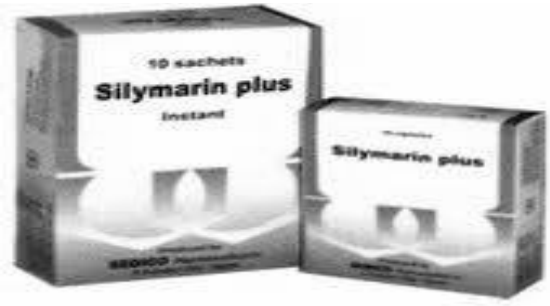
2-Hepamarin cap.>>>hepatic cell protective

3-Hepaticum cap.& susp. >>>protective &activator

Silymarin with compilation:

1-Silipex:>>>silymarin and lecithin complex.

2-silymarin plus Eff. & Cap. >>silymarin+ acetylcysteine + zinc



3-Hipamax plus Cap.>>>silymarin +glutathione &lecithin

4-Simepar tab. :>>>silymarin & Vit $B_{1,2,3,5,6,12}$

Ursodeoxycholic acid

Ursodeoxycholic acid is a choleretic agent, as all bile acids, but differs from other di-hydroxy-bile acids in being non-cytotoxic because it has less affinity for membranes, and when present at micellar concentrations does not solubilize membranes.

Mode of action:

Promotes the dissolution of non calcified ,floating cholesterol gallstones .

It increases the total bile acid pool and inhibits HMGCoA reductase activity.

The resultant cholesterol of unsaturation enhances the capacity of bile to dissolve cholesterol of gallstone.

 INTERACTIONS : Estrogen oral contraceptives & lipid lowering agents increase hepatic cholesterol secretion &encourage cholesterol gallstone formation & hence may counteract Ursodiol effect.

Its dose:

DOSE : 1- for gall stone dissolution 8-10mg./kg. body weight as single dose at bedtime or divided into 2 doses.

2- for gallstone prevention 600mg./day in two divided doses.

3- chronic hepatitis & cholestatic liver diseases 10-15mg./kg body weight divided into 2-4 doses.

Brand Names:

1-Ursofalk Cap. >>>

2-Livagoal Cap.- >>>

It is the name of :"Name Thiazolidine-4-carboxylic acid".

Mode of action:

active against thimerosal intoxication; acts on cell membranes of tumor cells causing reverse transformation to normal cells.

It acts as : anti arrhythmic- anti oxidant & anti neoplastic agent.

It uses in chronic hepatitis , cirrhosis & fatty liver.

Brand Names:

1-Hepaton tab.>>>

2-Heparegen Tab>>>

L-ornitine-L-asparate

This medication is prescribed for the treatment of high ammonia levels or severe liver impairment. It is also used for end-stage cirrhosis.

Mode of action:

It provides critical substrates for ureagenesis and glutamine synthesis, the two primary mechanisms by which the body rids itself of excess ammonia. Ornithine is a specific activator of ornithine carbamyl transferase and carbamylphosphate synthetase, and, in addition, is a substrate for ureagenesis. These reactions are carried out mainly in the periportal portion of the hepatic lobules. Aspartate and ornithine, after conversion to alfa-ketoglutarate, are substrates for glutamine synthesis, which is performed exclusively by a small population of perivenous hepatocytes, the so-called perivenous scavenger cells. The ammonia lowering effect resulting from the stimulation of these two basic mechanisms of ammonia detoxification has been studied in animals and was confirmed in humans in clinical trials.

ℵ Precautions :

*Contraindicated in patients with elevated level of liver enzymes.

*It comes as a tablet and liquid to take by mouth with or without food.

* Caution needed for pregnant and breastfeeding women.

* AS Side Effects : Transient nausea and vomiting.

Brand Names:

1-Hepa- Merz Sach

2-Merzinoleve

Sorbitol

Sorbitol is chemically designated D-glucitol ($C_6H_{14}O_6$).

Sorbitol, an isomer of mannitol, is a hexitol naturally occurring in many fruits, and is produced commercially by the reduction of glucose.

Mode of action:

It has laxative effect, it enhance secretion of fresh bile and normalize intestine function .

So, it used as activator for bile^_^

EX. Of Brand Name:

1-Sorbit Sach.>>>

2-sorbitol Sach.>>>

¥There are other drugs used to support the liver function.

Ex.: Heparsan- Farcovit B12-liv plus ….etc.

Patient counseling

The our role as pharmacists not only give medication ,but also give the patient advices, information ,and help him for healthy care.

Some advices for hepatitis patient:

1-Do not share needle. -

2-D not share drug equipment.

3-Do not donate blood.

4-must use condom in sexual process.

5-Stop using alcohol & smoking.

6-See your doctor regularly.

7-Don't start any new medicines or use over-the-counter, herbal, and other medicines without a physician's knowledge.

8-Get vaccinated against hepatitis A if liver damage is present.

9-Avoid drugs as acetaminophen, ibuprofen , ketoprofen ,and aspirin.

10-Decrease salt food content and take diuretics to protect him self from edema.

11-Decrease proteins in take and avoided the hyponetics and sedatives. He can take vitamins .

REFRANCES

Sites:

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